

Amendment After Final dated November 4, 2008  
Response to Final Office Action dated September 4, 2008

### REMARKS

Applicant respectfully requests reconsideration. Claims 1, 2, 5-7, 9, 11-17, 19-34, 68, 91, 125, 126 and 128-130 were previously pending in this application. By this amendment, claims 1, 2, 68, 91, 125, 126, 129 and 130 have been amended. Support for the amendment can be found in the written description at least on page 2, lines 3-18 and Figure 1. No claims have been cancelled or added. As a result, claims 1, 2, 5-7, 9, 11-17, 19-34, 68, 91, 125, 126 and 128-130 are pending for examination with claims 1, 68, 91, 125, 126, 129 and 130 being independent claims. No new matter has been added.

### Rejections under 35 U.S.C. §102

Claims 1, 2, 5-7, 11, 14, 16, 24-26, 31, 91, 126, 128 and 129 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Cheng et al. (Biochemical and Biophysical Research Communications (1991) 174(2): 785-789). According to the Examiner, Cheng et al. teaches a method for analyzing a nucleic acid polymer, including all the limitations of claims 1, 2, 5-7, 11, 14, 16, 24-26, 31, 91 and 126-129.

Applicant respectfully disagrees. Cheng et al. does not teach all the steps of the rejected claims and therefore Cheng et al. does not anticipate the rejected claims. The methods of the rejected claims recite a step of “providing a conjugate” and a step of “contacting a nucleic acid polymer with the conjugate”. The Examiner reasons on pages 23-24 of the Office Action that the claims as written do not require the step of providing the conjugate to occur before the step of “contacting a nucleic acid with the conjugate”. However, the Examiner’s reasoning is incorrect. Firstly, the claims require the “providing” step to precede the “contacting” step. One cannot contact with something that has not been provided. Secondly, based on the use of “a conjugate” in the providing step and the use of “the conjugate” in the contacting step, it is clear that the providing step needs to occur first, because otherwise there would be no antecedent basis for “the conjugate” in the contacting step. Nevertheless, without conceding the Examiner’s position and merely in the interest of expediting prosecution, Applicant has amended independent claims 1, 91, 126 and 129 to recite a first step, second step and, in some claims, a third step in order to explicitly recite the order of these steps.

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The claims as amended provide a first step of “providing a conjugate” and a second step of “contacting a nucleic acid polymer with the conjugate”. Cheng et al. does not teach a first step of “providing a conjugate” and second step of “contacting a nucleic acid polymer with the conjugate”. Cheng et al. teaches a first step of contacting an HIV-reverse transcriptase that is not covalently conjugated to a nucleic acid with a primed nucleic acid and a second step of crosslinking the HIV-reverse transcriptase to the primed nucleic acid. Thus, Cheng et al. teaches a first step of “contacting a nucleic acid with an enzyme” and a second step of “providing a conjugate”. Cheng et al. does not provide all the limitations of the rejected claims and it therefore does not anticipate such claims.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claim 125 is rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 6,362,328 to Fisher et al. as evidenced by Chaudhry et al. (Nucleic Acids Research (1995) 23(19): 3805-3809). According to the Examiner, Fisher et al. teaches a method of analyzing a nucleic acid polymer using a covalent conjugate of an oligonucleotide and a nuclease. The Examiner relies on Chaudhry et al. for the teaching that a nuclease is a repair enzyme.

Applicant respectfully disagrees. However, without conceding the Examiner’s position and merely in the interest of expediting prosecution, Applicant has amended claim 125 to positively recite binding of a nucleic acid binding enzyme to a nucleic acid polymer non-specifically.

Fisher et al. does not teach all the steps of the method of the rejected claims as amended because Fisher et al. does not teach binding of the nucleic acid binding agent to the nucleic acid polymer non-specifically. In addition, Fisher et al. clearly states that the nuclease within the conjugate functions as a label. Fisher et al. repeatedly refers to the nucleic acid probe as a “single binding member”, thereby stating that the conjugate comprises only *one* nucleic acid binding member and that binding member is not the nuclease. Because Fisher et al. does not teach all the limitations of the rejected claim, Fisher et al. does not anticipate the rejected claim.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

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Rejections under 35 U.S.C. §103

Claims 1, 2, 5-7, 9, 11-15, 21-28, 30, 31, 91, 126, and 128-130 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Fisher et al. (U.S. Patent No. 6,362,328) as evidenced by Chaudhry et al. (Nucleic Acids Research (1995) 23(19): 3805-3809) in view of Kigawa et al. (U.S. Patent No. 5,965,361). According to the Examiner, Fisher et al. teaches a method for analyzing a nucleic acid polymer comprising all the limitations of the rejected claims, except for a method that does not depend on the catalytic activity of a nuclease and a method for labeling a nucleic acid tag molecule and a nucleic acid binding enzyme with detectable moieties. According to the Examiner, Kigawa et al. teaches methods of analyzing a nucleic acid polymer that do not rely on the catalytic activity of a nucleic acid binding enzyme and labeling with detectable moieties. Also, according to the Examiner, it would have been obvious to apply the teachings of Kigawa et al. to Fisher et al. because combining the teachings would result in a faster and simpler method for labeling a nucleic acid polymer. Finally, according to the Examiner, an ordinary artisan would have a reasonable expectation of success because the methods of Kigawa et al. and Fisher et al. are directed to the same problem.

Applicant respectfully disagrees. The combination of the teachings of Fisher et al. and Kigawa et al. does not render obvious the methods of the rejected claims for the reasons set forth below. However, without conceding the Examiner's position and merely in the interest of expediting prosecution, Applicant has amended claims 1, 91, 126 and 129 and 130 to positively recite binding of a nucleic acid binding enzyme to a nucleic acid polymer non-specifically.

The Examiner has not met her burden in establishing a *prima facie* obviousness rejection. The Supreme Court in *KSR* stated that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." The Examiner's reasoning is based on a faulty interpretation of the teachings of Fisher et al. The Examiner reasons that it would be obvious to one of ordinary skill in the art to label the nuclease of Fisher et al. with a detectable label, as taught by Kigawa et al. However, the teachings of Fisher et al. pertain to "the use of P1 and S1 nucleases as enzyme labels for assays" (column 2, lines 55-56). Because the enzyme already functions as a label, a person of ordinary skill in the art would have no

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reason to attach another label to such an enzyme. Thus, no rationale is provided for combining the teachings of Fisher et al. and Kigawa et al.

Furthermore, even if one of ordinary skill in the art would have found some reason to combine the references along the lines set forth in the Office Action, the combination of Fisher et al. and Kigawa et al. does not teach all the elements of the rejected claims, as amended. As discussed above, Fisher et al. does not teach that the nucleic acid binding agent binds to the nucleic acid polymer non-specifically. Kigawa et al. does not provide this missing teaching. Kigawa et al. teaches detection of specific nucleic acid structures and it is silent on nucleic acid binding agents that bind to nucleic acid polymers non-specifically. Thus, the combination of Fisher et al. and Kigawa et al. does not teach all limitations of the rejected claims.

Finally, a person of ordinary skill in the art would have no reasonable expectation of success in combining Fisher et al. and Kigawa et al. Fisher et al. teaches the use of enzyme labels which provide an amplified signal. In contrast, Kigawa et al. teaches the use of fluorescent labels, which provide a linear signal. A person of ordinary skill in the art would not expect that replacement of an amplified signal with a linear signal would provide similar or better background signal and/or detection limit. Thus, a person of ordinary skill in the art would have no reasonable expectation of success in combining Fisher et al. and Kigawa et al.

Applicant notes that claim 126 already contained the limitation “wherein the nucleic acid binding agent binds to the nucleic acid polymer non-specifically”. Based on the arguments presented by the Examiner, claim 126 should have not been included with the rejection.

For at least the reasons provided above, the combination of Fisher et al. and Kigawa et al. does not render obvious the rejected claims.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1, 2, 5-7, 9, 11-13, 16, 17, 22-31, 91, 126 and 128-130 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 6,362,328 to Fisher et al. as evidenced by Chaudhry et al. (*Nucleic Acids Research* (1995) 23(19): 3805-3809) in view of Rye et al. (*Nucleic Acids Research* (1992) 20(11): 2803-2812) and further in view of U.S. Patent No. 6,348,317 to Thompson et al.

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According to the Examiner, Fisher et al. teaches a method for analyzing a nucleic acid polymer but it does not teach labeling the nucleic acid polymer with a backbone specific label and labeling the nucleic acid tag molecule with a fluorophore agent or photocleaving agent. The Examiner relies on Rye et al. for the teaching of fluorescent intercalators that are backbone specific labels and photocleaving agents, as evidenced by Thompson et al.

Applicant respectfully traverses. The combination of Fisher et al., Rye et al. and Thompson et al. does not render obvious the rejected claims.

Firstly, the combination of Fisher et al., Rye et al. and Thompson et al. does not teach all the elements of the rejected claims, as amended. At a minimum, the combination does not teach a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding agent wherein the nucleic acid binding agent binds to a nucleic acid polymer non-specifically. As discussed above, Fisher et al. does not teach a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme wherein the nucleic acid binding agent binds to a nucleic acid polymer non-specifically. The teachings of Rye et al. and Thompson et al. relate to fluorescent dyes and do not supply the missing teachings.

Secondly, a person of ordinary skill in the art would have no expectation of success in combining the teachings of Fisher et al., Rye et al. and Thompson et al. The Examiner reasons on page 15 of the Office Action that the fluorescent intercalators of Rye et al. would have been faster and simpler than the enzyme labels taught by Fisher et al. However, the fluorescent intercalators of Rye et al. detect only double stranded nucleic acids, and certainly not enzymes. Furthermore, it is unclear how a pattern of binding of the conjugate to the nucleic acid polymer could be determined if the nucleic acid polymer was itself labeled with the same moieties. Finally, the fluorescent labels of Rye et al. provide a linear signal while the enzyme labels of Fisher et al. provide an amplified signal, and thus these labels are not readily interchangeable, as discussed above. A person of ordinary skill in the art would therefore have no reasonable expectation of success when combining the teachings of Fisher et al., Rye et al. and Thompson et al.

Thus, at least for the reasons presented above, the combination of Fisher et al., Rye et al. and Thompson et al. does not render obvious the rejected claims.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

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Claims 19, 20, 33, and 34 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 6,362,328 to Fisher et al. as evidenced by Chaudhry et al. (*Nucleic Acids Research* (1995) 23(19): 3805-3809) in view of U.S. Patent No. 5,965,361 to Kigawa et al. and further in view of PCT Publication No. WO 00/09757 to Tegenfeldt et al.

According to the Examiner, the combination of Fisher et al., Chaudhry et al. and Kigawa et al. teaches all the limitations of the rejected claims, except for a linear polymer analysis system for optically analyzing polymers. The Examiner relies on Tegenfeldt et al. for the teaching of a linear polymer analysis system.

Applicant respectfully traverses. The combination of Fisher et al., Chaudhry et al., Kigawa et al. and Tegenfeldt et al. does not render obvious the rejected claims, as amended, at least because the combination does not teach all the elements of the rejected claims. At a minimum, the combination does not teach a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding agent wherein the nucleic acid binding agent binds to a nucleic acid polymer non-specifically.

As discussed above, the combination of Fisher et al., Chaudhry et al., and Kigawa et al. does not teach a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding agent wherein the nucleic acid binding agent binds to a nucleic acid polymer non-specifically. Tegenfeldt et al. does not supply the missing teaching. Thus, for at least this reason, the combination of Fisher et al., Chaudhry et al., Kigawa et al. and Tegenfeldt et al. does not render obvious the rejected claims.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claim 32 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 6,362,328 to Fisher et al. as evidenced by Chaudhry et al. (*Nucleic Acids Research* (1995) 23(19): 3805-3809) in view of U.S. Patent No. 5,965,361 to Kigawa et al. and further in view of Gite et al. (*Journal of Molecular Recognition* (1995) 8: 281-289).

According to the Examiner, the combination of Fisher et al., Chaudhry et al. and Kigawa et al. teaches all the limitations of the rejected claim, except for detecting the nucleic acid binding enzyme using an antibody. The Examiner relies on Gite et al. for the teaching of detecting a nucleic acid binding enzyme using an antibody.

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Applicant respectfully traverses. The combination of Fisher et al., Chaudhry et al., Kigawa et al. and Gite et al. does not render obvious the rejected claim, as amended, because the combination does not teach all the elements of the rejected claim. At a minimum, the combination does not teach a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding agent wherein the nucleic acid binding agent binds to a nucleic acid polymer non-specifically.

As discussed above, the combination of Fisher et al., Chaudhry et al., and Kigawa et al. does not teach a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding agent wherein the nucleic acid binding agent binds to a nucleic acid polymer non-specifically. The teachings of Gite et al. relate to detecting a nuclease using an antibody. Gite et al. does not supply the missing teachings. Thus, for at least this reason, the combination of Fisher et al., Chaudhry et al., Kigawa et al. and Gite et al. does not render obvious the rejected claim.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claim 68 is rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,362,328 to Fisher et al. in view of U.S. Patent No. 5,965,361 to Kigawa et al. and further in view of PCT Publication No. WO 00/09757 to Tegenfeldt et al.

According to the Examiner, the combination of Fisher et al., and Kigawa et al. teaches all the limitations of the rejected claim, except for a linear polymer analysis system for optically analyzing polymers. The Examiner relies on Tegenfeldt et al. for the teaching of a linear polymer analysis system.

Applicant respectfully disagrees. Applicant has amended claim 68 and introduced the limitation “wherein the nucleic acid binding agent binds to a nucleic acid polymer non-specifically”. The combination of Fisher et al., Kigawa et al. and Tegenfeldt et al. does not render obvious the rejected claim, as amended, at least because the combination does not teach all the elements of the rejected claim. At a minimum, the combination does not teach a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding agent wherein the nucleic acid binding agent binds to a nucleic acid polymer non-specifically.

As discussed above, the combination of Fisher et al., and Kigawa et al. does not teach a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding agent wherein the

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nucleic acid binding agent binds to a nucleic acid polymer non-specifically. Tegenfeldt et al. does not supply the missing teaching. Thus, for at least this reason, the combination of Fisher et al., Kigawa et al. and Tegenfeldt et al. does not render obvious the rejected claims.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

### **CONCLUSION**

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No.: C0989.70054US00.

Respectfully submitted,

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